Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

ART
Advanced Radiation Therapy

Utilizzo non convenzionale dell'Imaging in Radioterapia

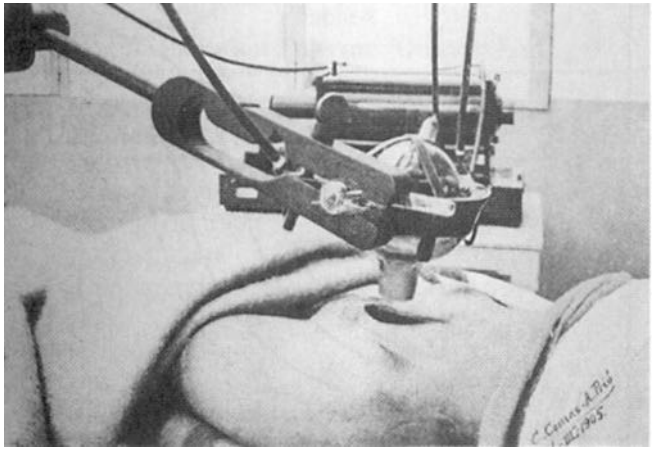
Chieti, 24 febbraio 2017

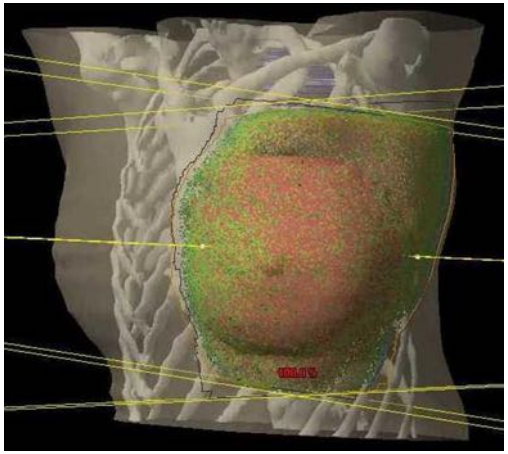
Dr. Luca Boldrini

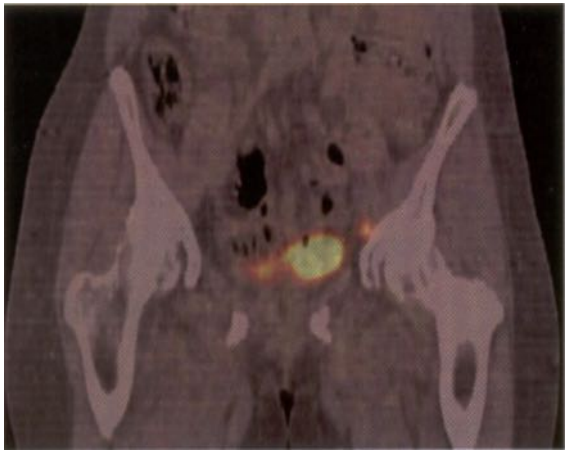
Datamining
Radiomics

KBO Labs
Knowledge Based Oncology Labs

Conventional







Role of imaging in Radiation Oncology

Diagnosis

Staging : locoregional, systemic

Characterization : Mp imaging, IB, hybrid approaches

Prognostic evaluation

Conventional Radiation Oncology purposes

- segmentation
- planning
- delivery, motion management and adaptive approach
- acute toxicity

Follow up : response, relapse and late toxicity

Theragnostics

The use of **diagnostics**

to tailor therapeutic approaches

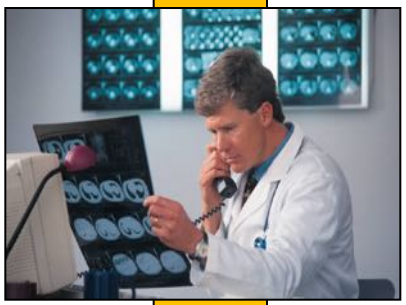
thus **facilitating**

personalized medicine

Bentzen S. - Lancet Oncology 2005

Theragnostic imaging paradigm

BEFORE



Diagnosis
Staging

Target volumes & Planning

DURING

In room imaging (IGRT)

Off-line / On-line

Theragnostic Imaging

(biologically adapted prescription)

AFTER

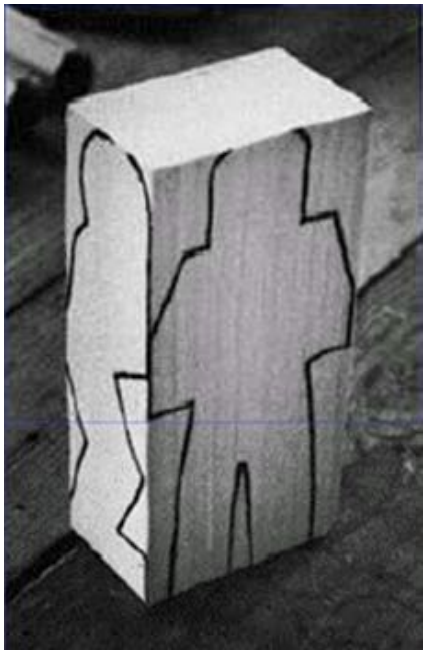
Response evaluation

Tumor recurrence

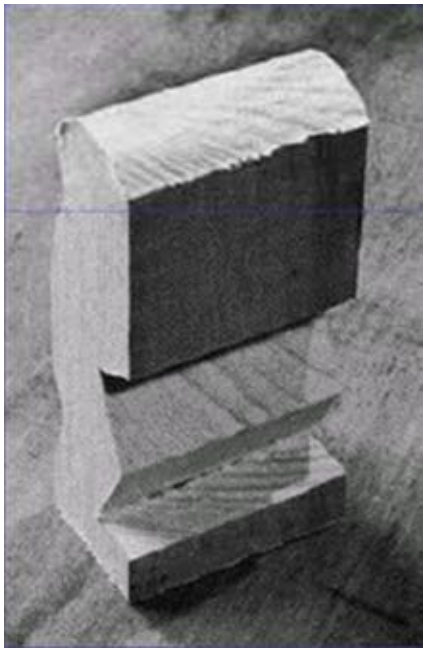
Late toxicity

Modified from Bentzen S. - Lancet Oncology 2005

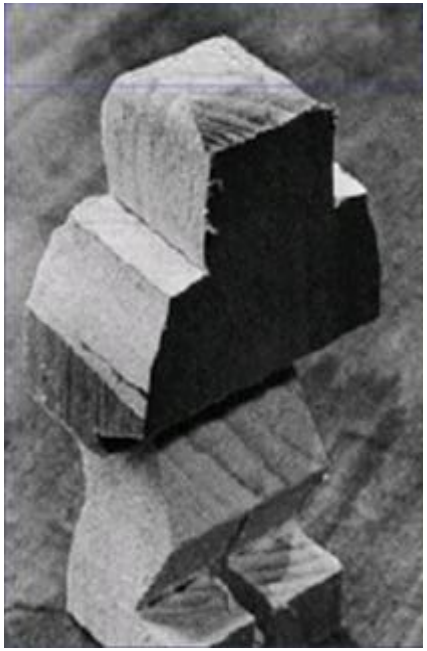
High technology opportunities



2 D Planning



3 D Planning

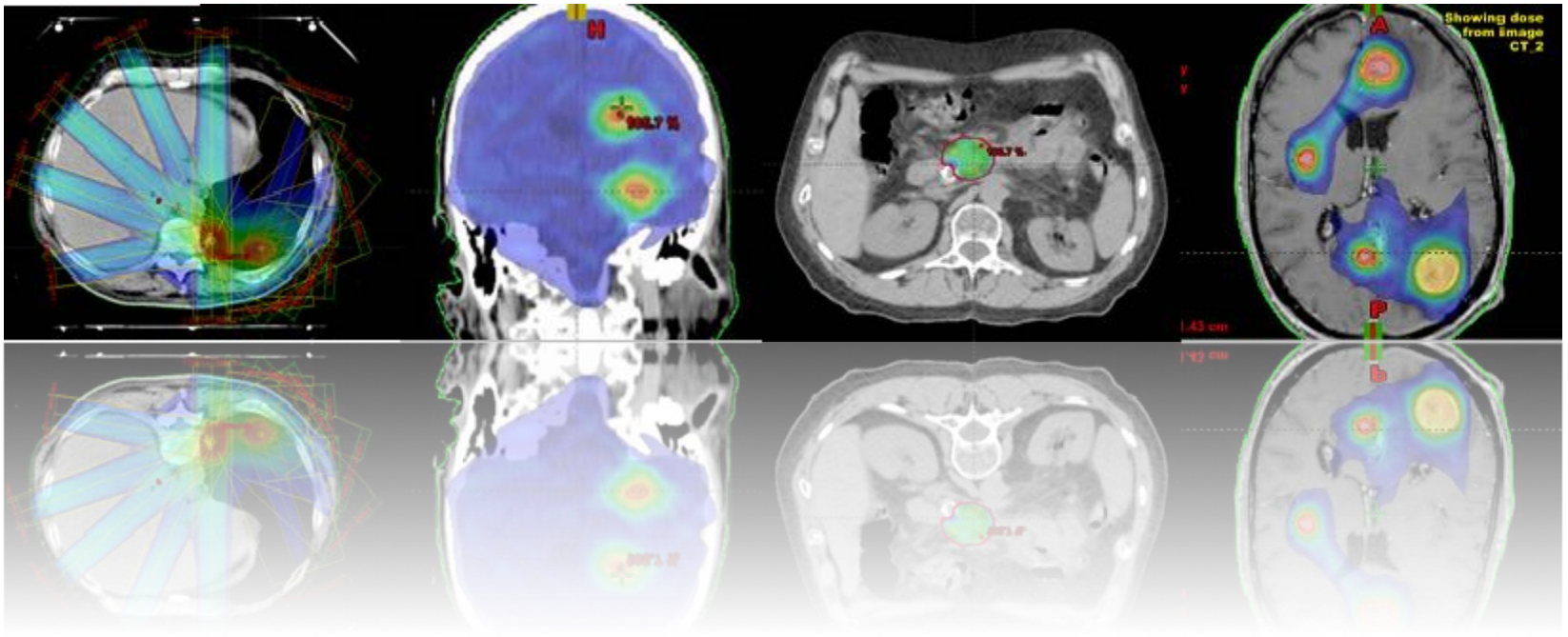


IMRT Planning

Dose sculpting

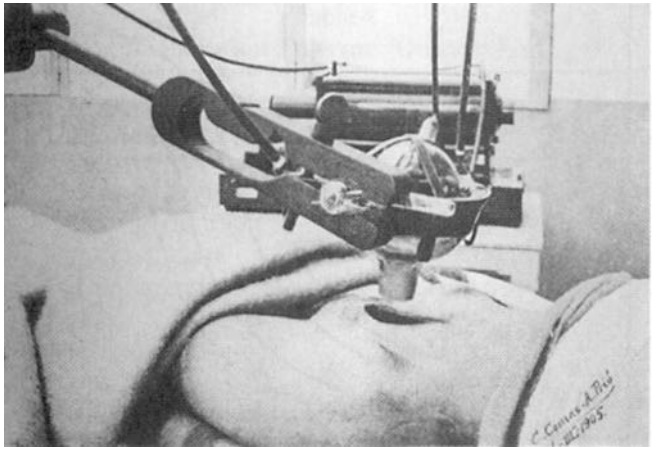
Courtesy of Verellen D. - 2013

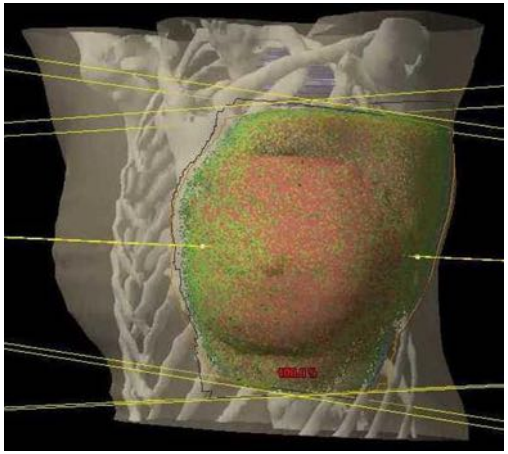
High technology opportunities

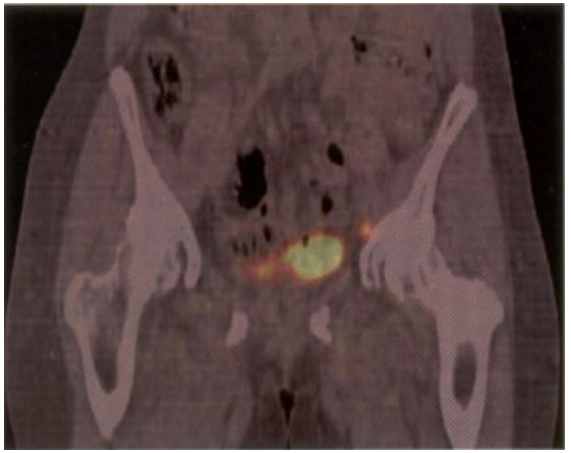


Towards small (and differently visible) target volumes

UNconventional







In-room MRI: the great challenge

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Magnetic Resonance–Guided Adaptive Radiotherapy: A Solution to the Future

Patrick Kupelian, MD,* and Jan-Jakob Sonke, PhD†

Magnetic resonance imaging–guided adaptive radiotherapy would make available the best in anatomical and functional imaging during the course of radiation therapy. The possible methodology of magnetic resonance imaging–guided adapted radiotherapy and possible clinical applications are discussed.

Semin Radiat Oncol 24:227-232

MRI-RT: an hybrid answer

Main objective: higher dose delivery to targets and toxicity reduction with organs at risk sparing through image optimization

Metabolic and functional imaging: new targets, dose painting, new toxicity paradigms

Adaptive therapy: intra- interfraction, movement management, autosegmentation

MRI-RT: the great challenge

MRI in treatment room requires a fully integrated solution:

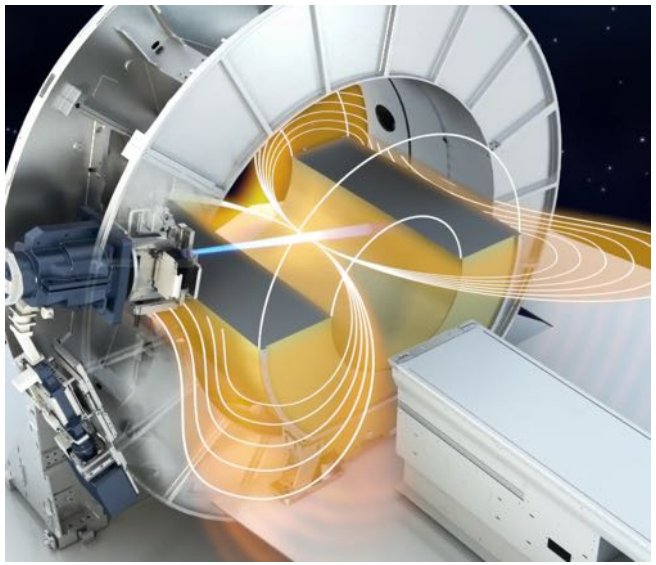
1. MRI – Linac

designed in UMC – Utrecht

8 MV accelerator, FFF

Modified 1.5 T Philips Ingenia MRI

Linac mounted in ring around MRI

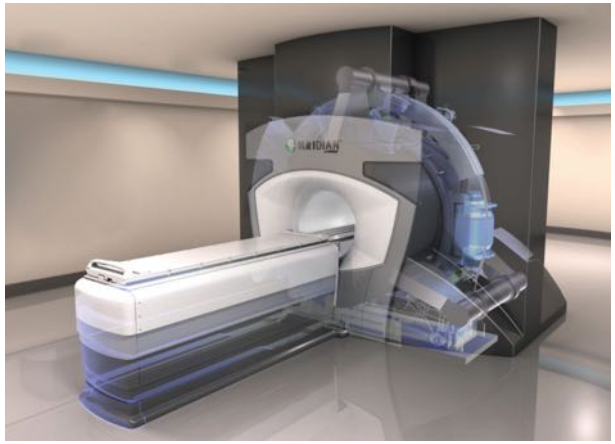


Raaymakers et al. Phys Med Biol -2009

Courtesy of Uulke van der Heide

MRI-RT: the great challenge

MRI in treatment room requires a fully integrated solution:



2. MRI – ^{60}Co

MRIdian® (ViewRay)

0.35 T MRI split magnet

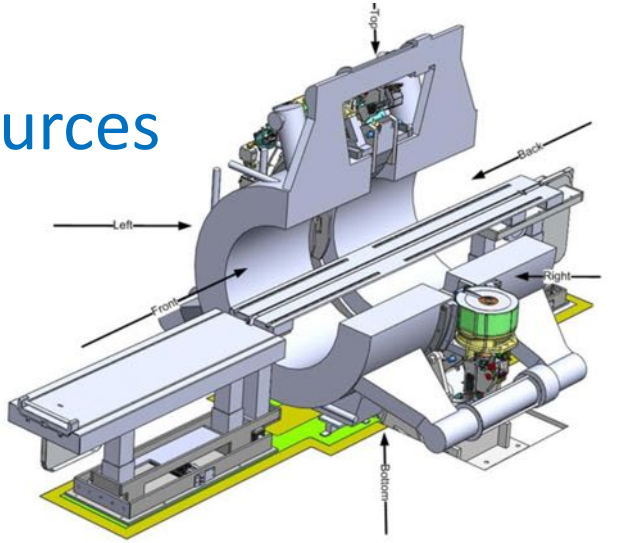
Real time imaging 4 frames per second

3 ^{60}Co heads (15.000 Ci each) on a ring gantry

Bore size : 69.3 cm

Primary collimators directly under the sources

MLC : 30 leaves




Treatment Controls
Pause
End Treatment Early
Treatment Status
BEAM OFF
Target In Bounds
Group 3 Isocenter
40.0° IMRT
Segments: 11 Beam-On: 31.5 sec
160.0° IMRT
Segments: 11 Beam-On: 24.6 sec
280.0° IMRT
Segments: 12 Beam-On: 46.9 sec
Group 4 Isocenter
Beams
Beam 1 Angle: 40.0
Segment of 11
Beam 2 Angle: 160.0
Segment of 11
Beam 3 Angle: 280.0
Segment of 12
Treatment Time
Total 325
Elapsed 0
Remaining 325
0 %
Head 1
Head 2
Head 3
Set
Elapsed
Primary
Secondary
Plan and Machine
Plan Type IMRT
Fraction Number 10
Fraction Primary Dose 1.76
Patient Orientation
Head First Supine
Actual
Target
Gantry Angle 136.0° 40.0°
Couch Lateral -0.2 cm -0.2 cm
Couch Vertical -10.8 cm -10.8 cm
Couch Longitudinal 229.4 cm 229.4 cm
System Status
Treatment Active
MRI Ready
RT Ready
Couch Ready
Gantry Ready
Door Fully Closed
For Research Use Only. Not for Human or Clinical Use.

MRI–^{60}Co RT: imaging features

Scan Name	Sequence Types	Function
Pilot Scan	GRE (3D) TRUFI (3D)	Localization of anatomy and patient positioning
Planning Scan	GRE (3D) TRUFI (3D) TFL (3D)	Treatment Planning
Treatment Scan	EPI (2D) GRE (2D) TRUFI (2D)	MRIS monitoring during treatment delivery
QA	SE (2D)	SNR, uniformity, contrast, and other QA functions

GRE: Gradient Echo - Proton density, T1, T2 - 2D GRE is 25 sec per image
TRUFI: TRUe Fast Imaging with steady state free precession – T1, T2 – 25 sec 3D planning/pilot, 0.25 sec treatment scan
TFL: Turbo Flash – T1, mix T1/T2 – 3 min
EPI: Echo Planar Imaging – T2, mix T1/T2 – 0.25 sec per frame
SE: Spin Echo

Courtesy of VIewRay: 00016 technical manual revG

^{60}Co MRI-IGRT: pitfalls and questions

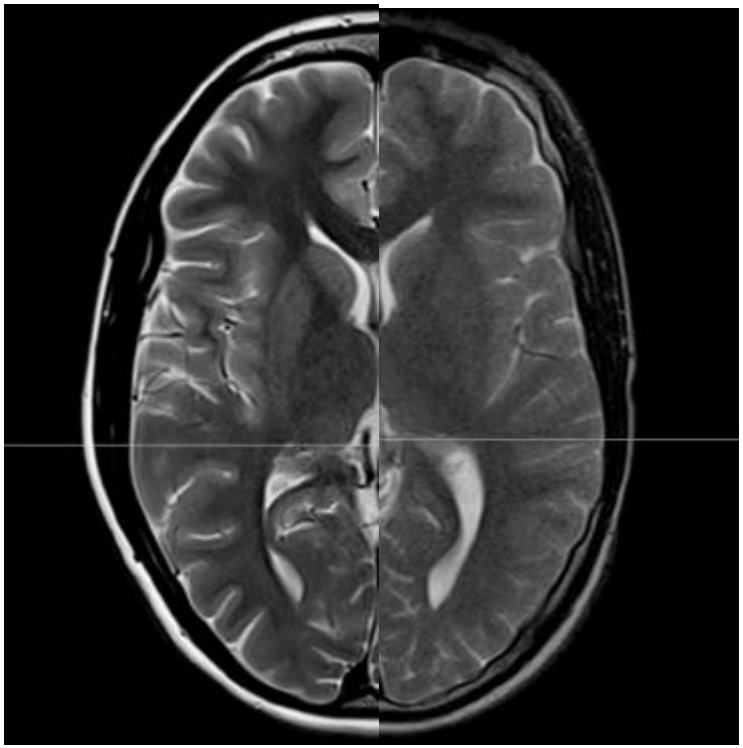
^{60}Co MRI IGRT: pitfalls and questions

- *Energy of of 60Co γ-rays lower than energy LINAC X rays*
  - *Collimation*
  - *Conformality*
  - *Coils attenuation*
  - *Magnetic field perturbation*
  - *Patient heating*

- *QA of delivery-tracking process*
  - *Image quality and distortion*
  - *Autocontouring*
  - *Registration (elastic or rigid)*
  - *Eventual replanning*

^{60}Co MRI IGRT: image quality

1.5 T



0.35 T

from http://www.healthcare.siemens.com

^{60}Co MRI-IGRT: pitfalls and questions

- *MRI for in-room imaging opens a new era in radiation treatment workflow*
- *This new technology brings many expectations and multiple critical issues*
- *Need to multi-centric cooperation, common lexicon for MRI-RT*
- *Possibility to have a new tool for prognostic evaluation during the treatment execution*
- *Need to create a robust QA for dose accumulation algorithms*
- *Evaluation of impact of accumulated doses on outcome prediction*

GAMMA team research topics

Gemelli Art MRI-RT team

Gamma.ITV
Gamma.Similarity
Gamma.Adaptive
Gamma.Radiomics

GAMMA.ITV: movement analysis

Deliverable: Measurement of Organ Motion

Collaboration: Specific metrics 3D/4D «Features» to MRIdian

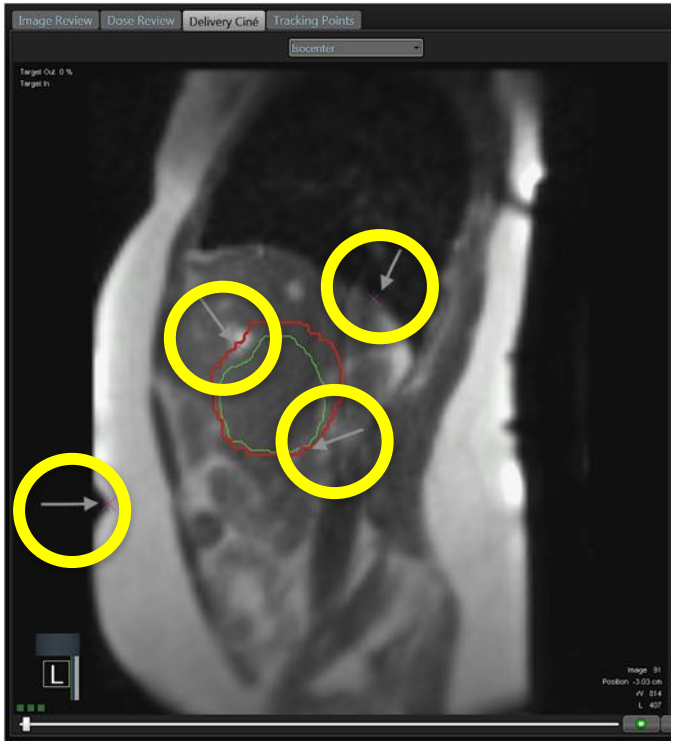



Image Review
Dose Review
Delivery Ciné
Tracking Points
Isocenter
Target Out 0 %
Target In
L

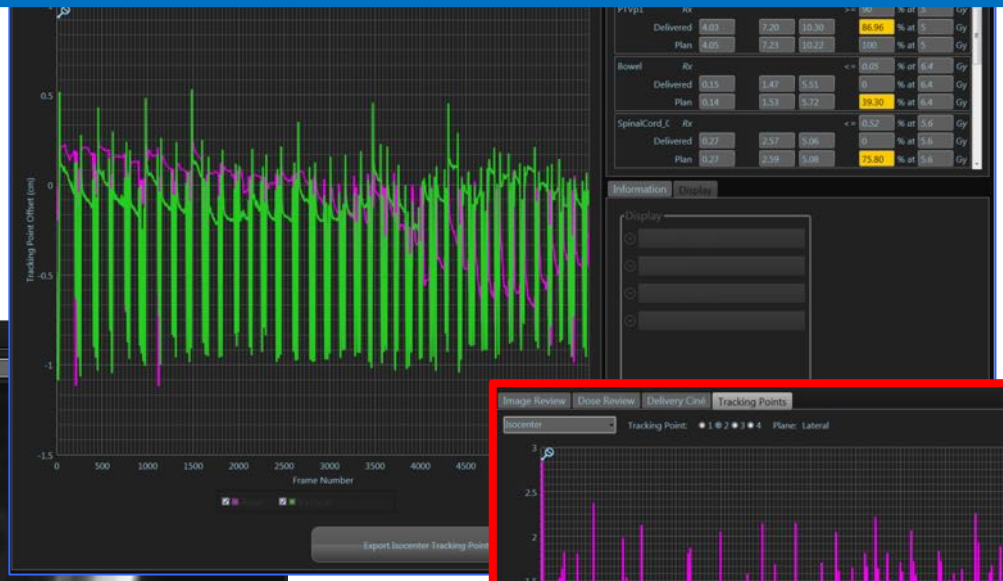
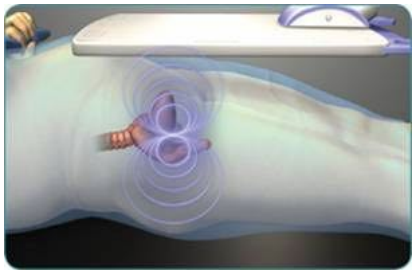

Tracking Point Offset (cm)
Frame Number
Export Isocenter Tracking Point


Image Review
Dose Review
Delivery Ciné
Tracking Points
Isocenter
Tracking Point: 1 2 3 4
Plane: Lateral
Tracking Point Offset (cm)
Frame Number
Export Isocenter Tracking Points To Text File
DVH
Plan-Rx Comparison
Statistics
Structure/Point
Min
Mean
Max
Dose to Volume
PTVp1
Bowel
SpinalCord_C
Delivered
Plan
Information
Display
PDF Report
Export Record
New Plan From Delivered
Save Dose

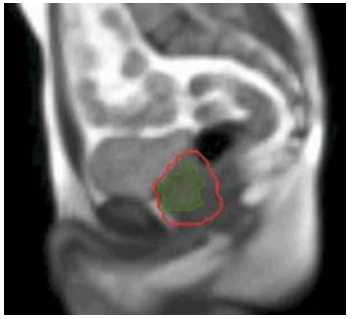

Image Review
Dose Review
Delivery Ciné
Tracking Points
Isocenter
Tracking Point: 1 2 3 4
Plane: Lateral
Tracking Point Offset (cm)
Frame Number
Information
Display

GAMMA.ITV: movement analysis

- *Organ motion (Target / OARs)*
- *Tailoring target volumes*
- *Comparative evaluation with different technologies*
- *Features definition for disease and patients candidate to MRIdian*
- *Specific metrics 3D/4D*



Calipso - VARIAN



MRIdian - VIEWRAY

GAMMA.SIMILARITY

Deliverable: *Acute toxicity comparison*

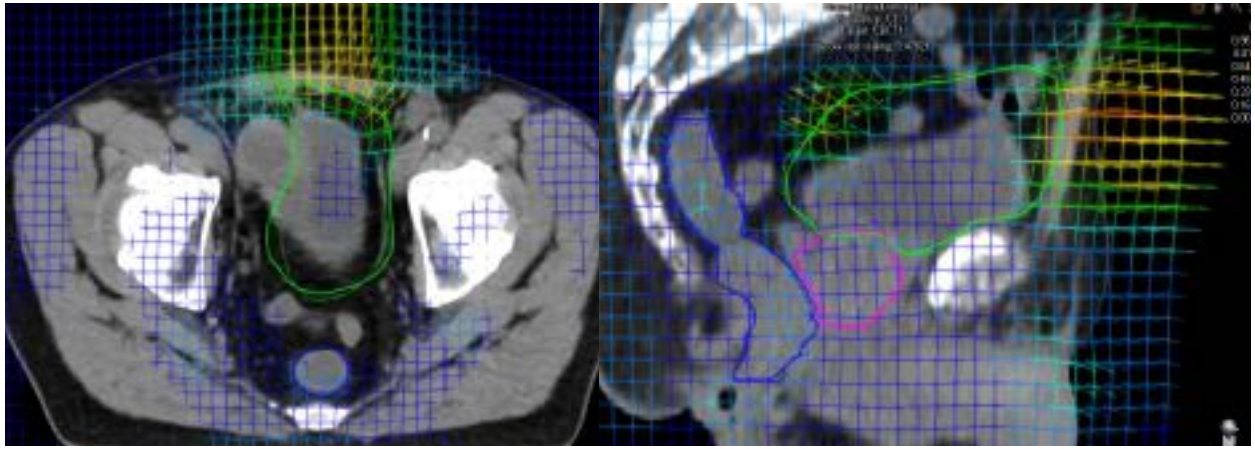
Collaboration: *Case Control Repository*

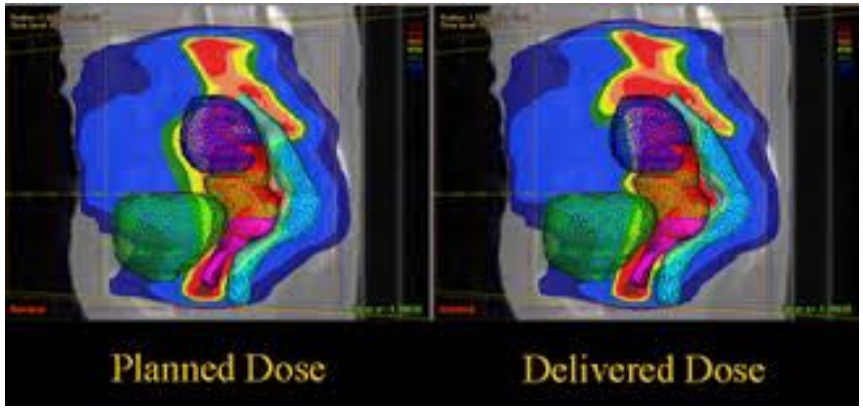
- *Specific metrics 3D/4D (geometrical/dosimetrical)*
- *Selection of case control with different technologies based on features for candidate to MRIdian*
- *Creation of a repository database (Multicentric)*
- *First endpoint to evaluate: acute toxicity comparison*

GAMMA.ADAPTIVE: Adaptive

Deliverable: Evaluation of dose accumulation

Collaboration: Dose Escalation/Reirradiation

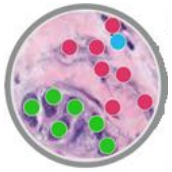




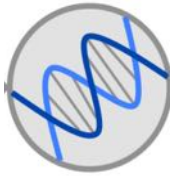
GAMMA.RADIOMICS

Deliverable: Radiomic analisys

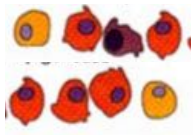
Collaboration: MRI DICOM Sharing



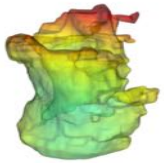
Biologico



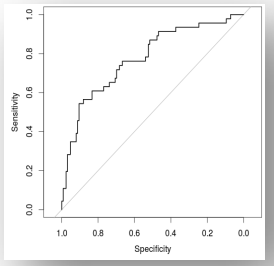
Genetico

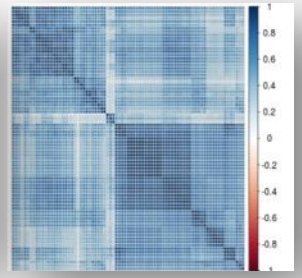


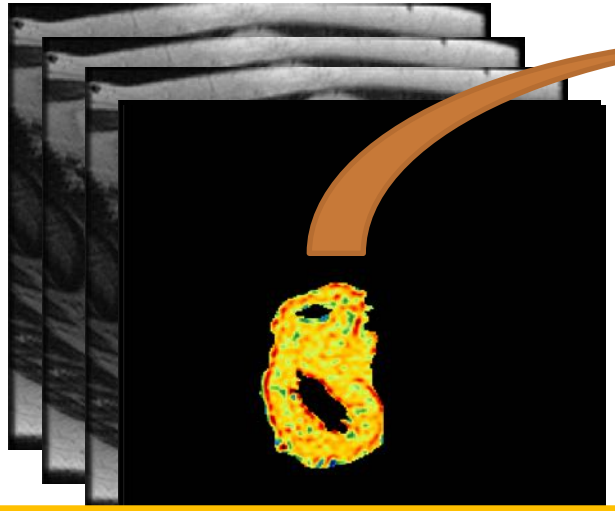
Fenotipico

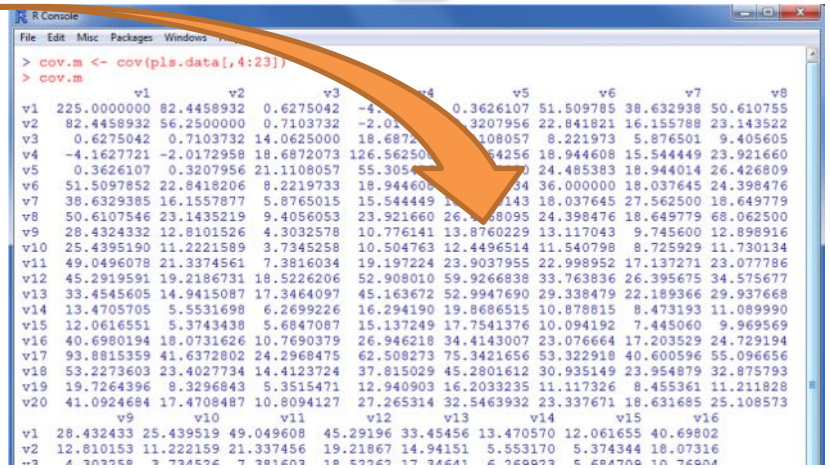


Radiomica









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v2	82.4458932	56.2500000	0.7103732	-2.01[illegible]	0.3207956	22.841821	16.155788	23.143522
v3	0.6275042	0.7103732	14.0625000	18.6872[illegible]	0.1108057	8.221973	5.876501	9.405605
v4	-4.1627721	-2.0172958	18.6872073	126.56250[illegible]	0.4254256	18.944608	15.544449	23.921660
v5	0.3626107	0.3207956	21.1108057	55.305[illegible]	0.0	24.485383	18.944014	26.426809
v6	51.5097852	22.8418206	8.2219733	18.94460[illegible]	0.4[illegible]34	36.000000	18.037645	24.398476
v7	38.6329385	16.1557877	5.8765015	15.544449	0.[illegible]143	18.037645	27.562500	18.649779
v8	50.6107546	23.1435219	9.4056053	23.921660	26.[illegible]8095	24.398476	18.649779	68.062500
v9	28.4324332	12.8101526	4.3032578	10.776141	13.8760229	13.117043	9.745600	12.898916
v10	25.4395190	11.2221589	3.7345258	10.504763	12.4496514	11.540798	8.725929	11.730134
v11	49.0496078	21.3374561	7.3816034	19.197224	23.9037955	22.998952	17.137271	23.077786
v12	45.2919591	19.2186731	18.5226206	52.908010	59.9266838	33.763836	26.395675	34.575677
v13	33.4545605	14.9415087	17.3464097	45.163672	52.9947690	29.338479	22.189366	29.937668
v14	13.4705705	5.5531698	6.2699226	16.294190	19.8686515	10.878815	8.473193	11.089990
v15	12.0616551	5.3743438	5.6847087	15.137249	17.7541376	10.094192	7.445060	9.969569
v16	40.6980194	18.0731626	10.7690379	26.946218	34.4143007	23.076664	17.203529	24.729194
v17	93.8815359	41.6372802	24.2968475	62.508273	75.3421656	53.322918	40.600596	55.096656
v18	53.2273603	23.4027734	14.4123724	37.815029	45.2801612	30.935149	23.954879	32.875793
v19	19.7264396	8.3296843	5.3515471	12.940903	16.2033235	11.117326	8.455361	11.211828
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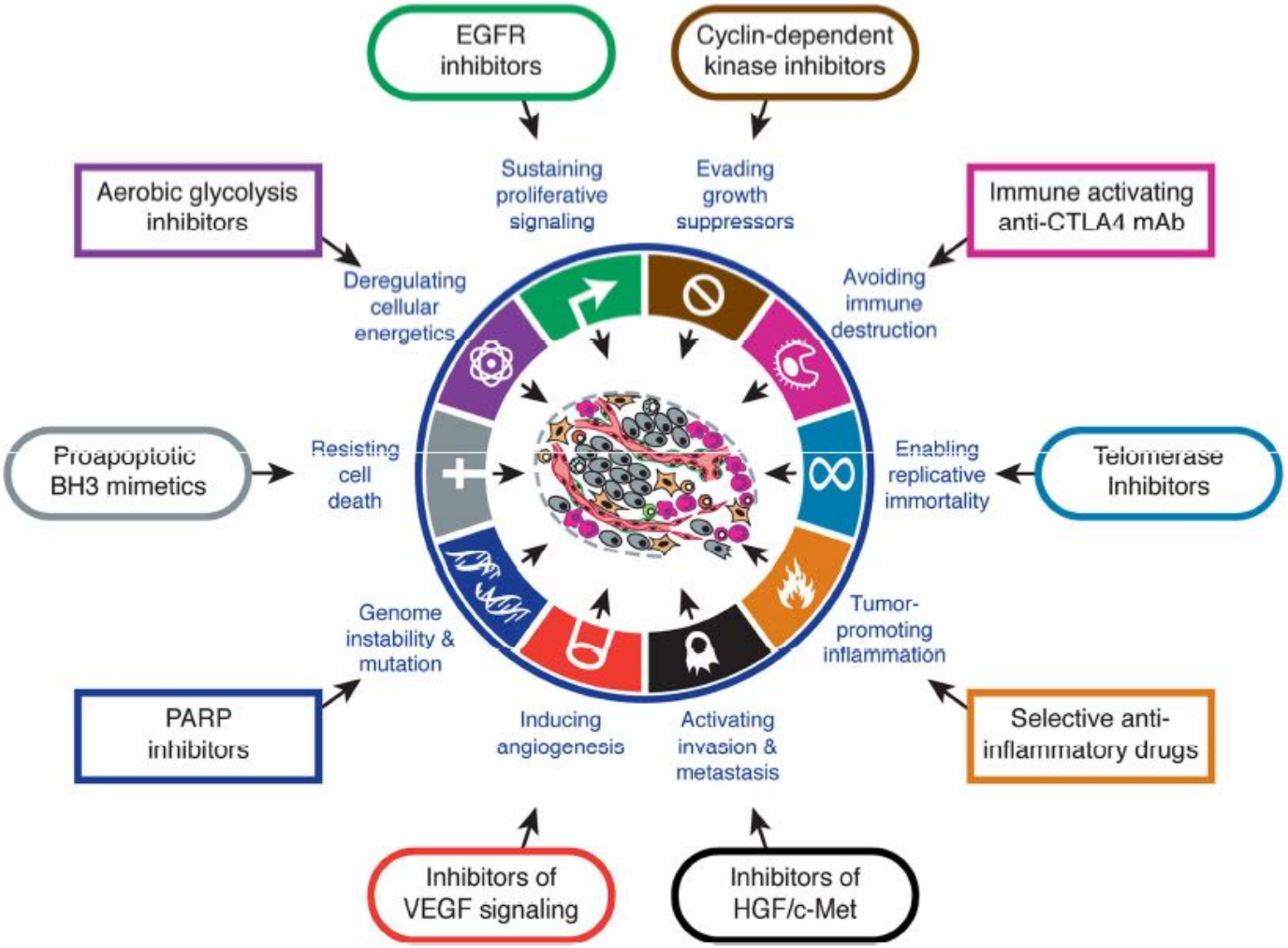
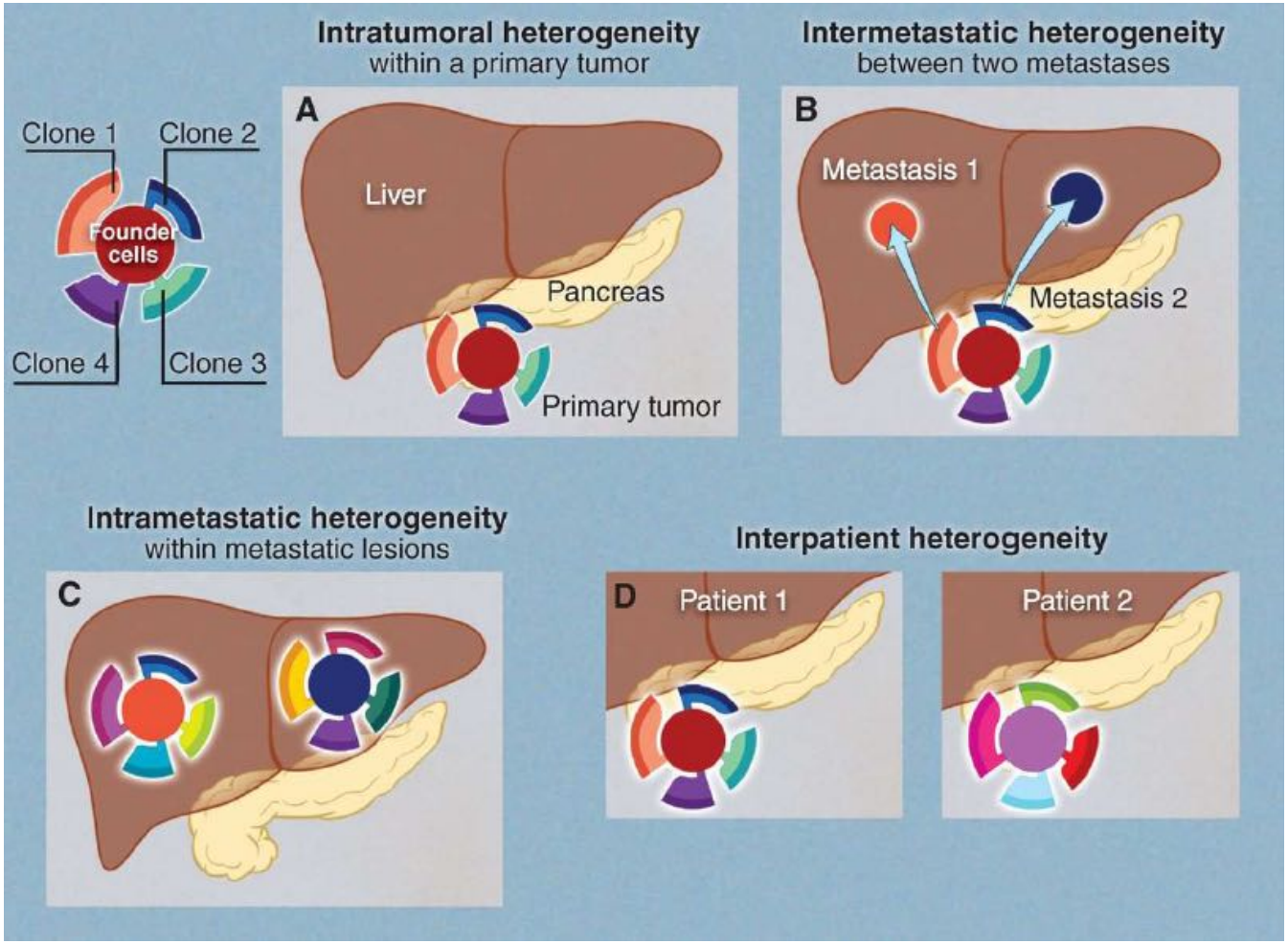
	v9	v10	v11	v12	v13	v14	v15	v16
v1	28.432433	25.439519	49.049608	45.29196	33.45456	13.470570	12.061655	40.69802
v2	12.810153	11.222159	21.337456	19.21867	14.94151	5.553170	5.374344	18.07316
v3	4.303258	3.734526	7.381603	18.53262	17.34641	6.269823	5.684709	10.76904

Much more than vessels and cells...



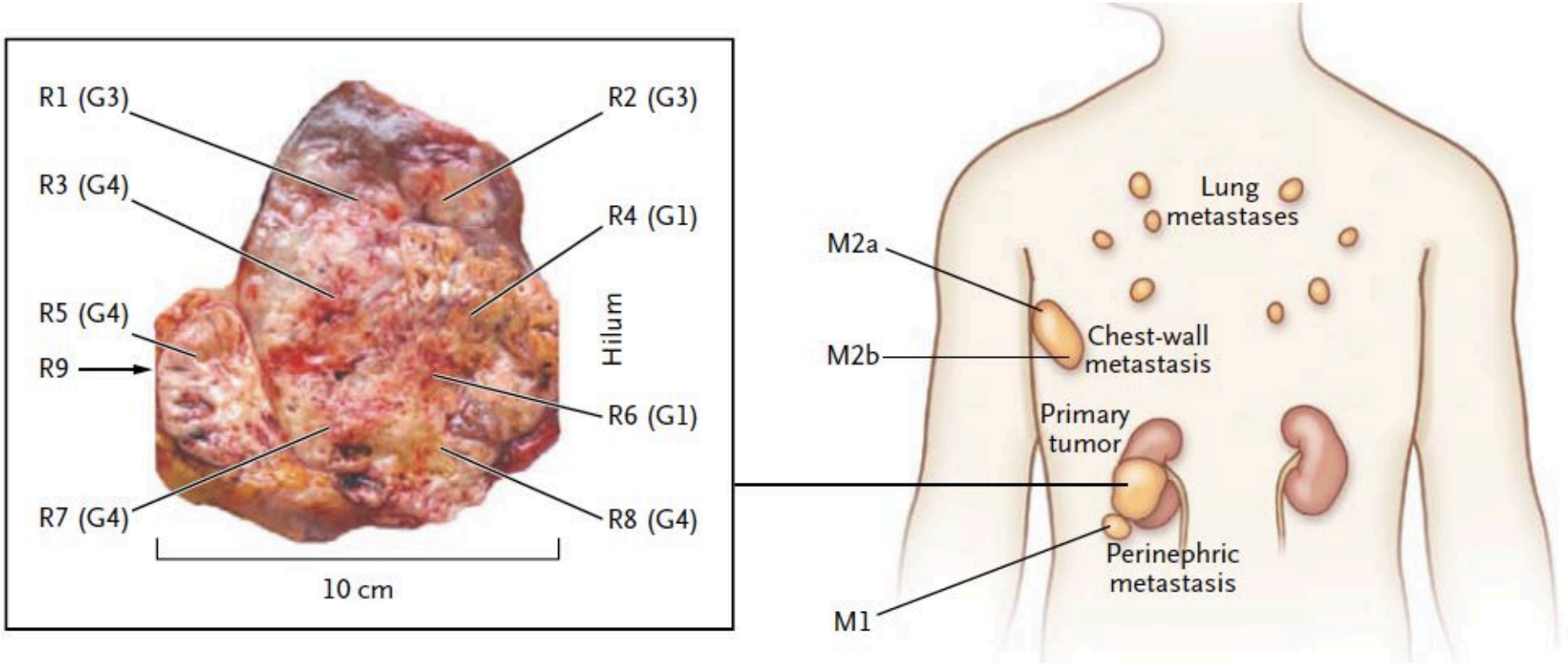
Hanahan D. and Weinberg RA. - Cell - 2011

Tumor heterogeneity

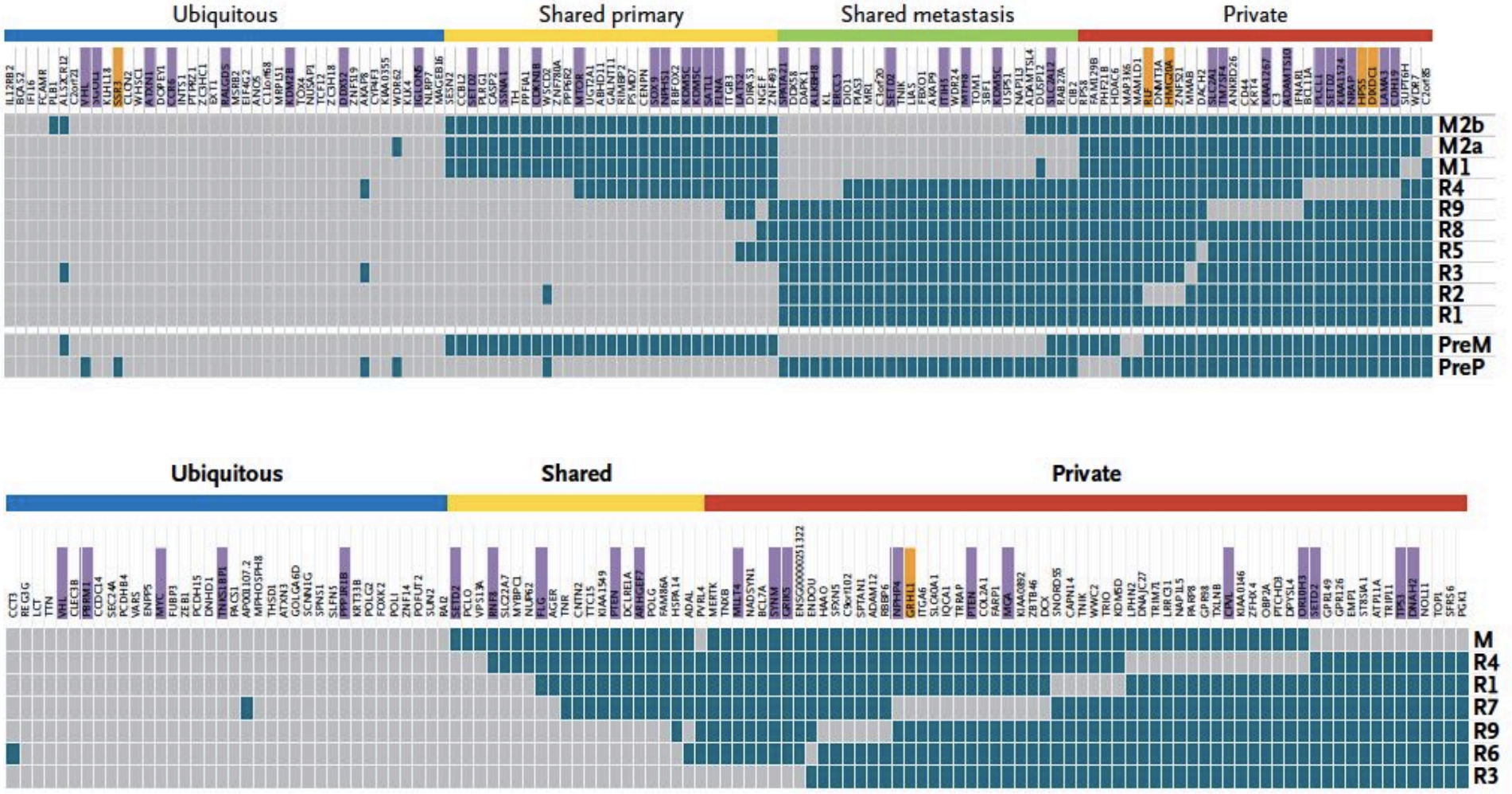


Vogelstein B. et al - Science - 2013

Tumor heterogeneity



Gerlinger M. et al - NEJM - 2012



Gerlinger M. et al - NEJM - 2012

Tumor heterogeneity

Tumor heterogeneity management

Tumor & treatments heterogeneity

Biomarkers

Non invasive

Low-cost

Reliable

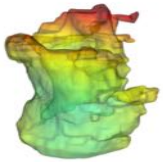
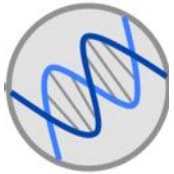
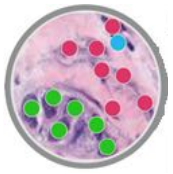
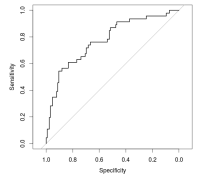
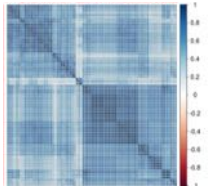
Easy

RADIOMICS

Radiomics

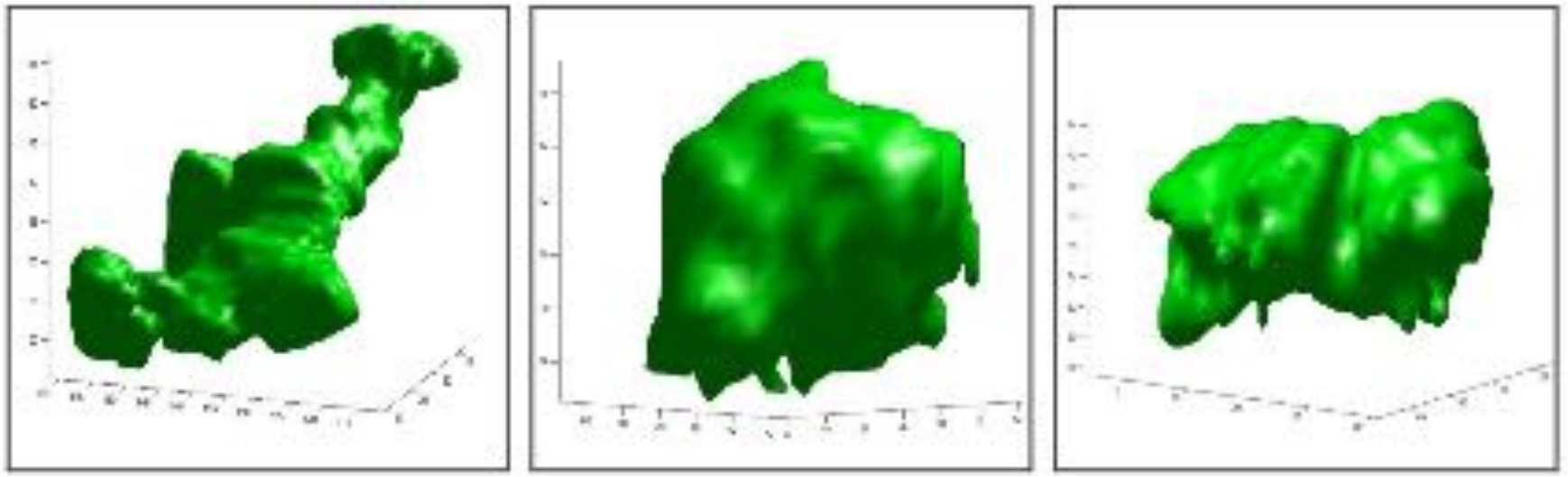
Radiomics is the process of **extraction of quantitative features** from **standard radiological imaging** for **clinical decision making** tool.

Texture Analysis, Histogram Analysis and **Morphometric Analysis** represent the three main approaches for **features extraction.**
Dedicated software needed.

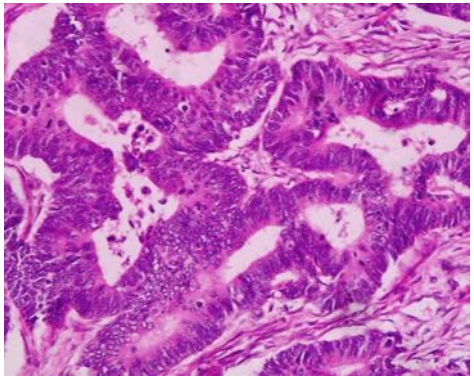
Lambin P. et al – Eur J Cancer - 2012

Radiomics: features extraction



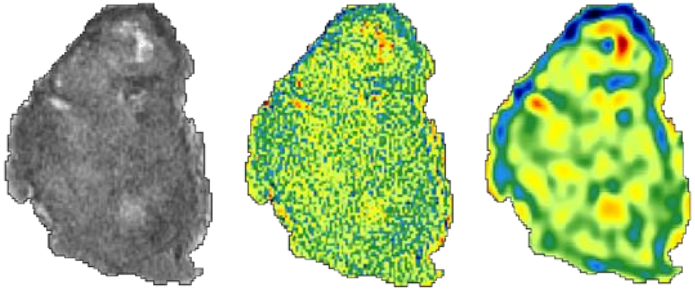
Lambin P. et al – Eur J Cancer - 2012

Histological evaluation



- Invasive
- Difficult to repeat
- Tumour sample not always are representative of the whole volume (tumor heterogeneity)
- Expensive

Radiomics evaluation



- Not invasive
- Repeatable
- Analyzes entire tumor volume
- Uses diagnostic exams already available
- Cheap

Radiomics analysis

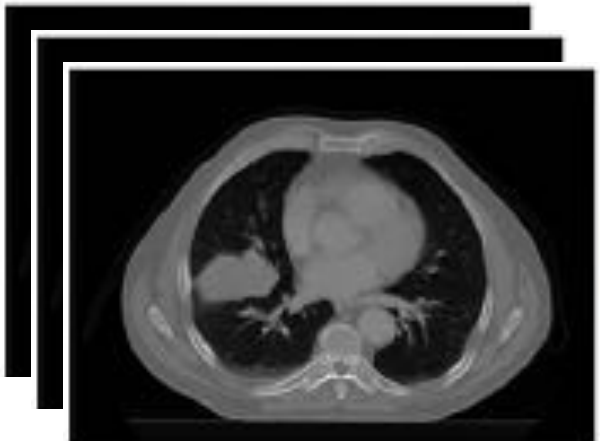
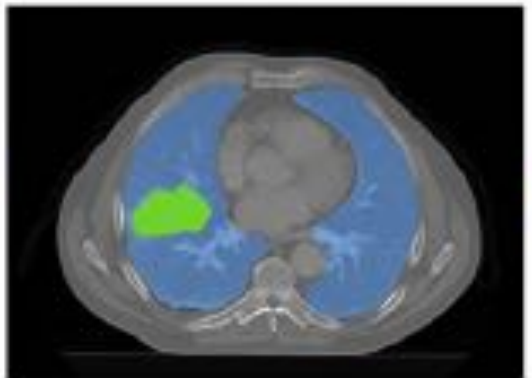
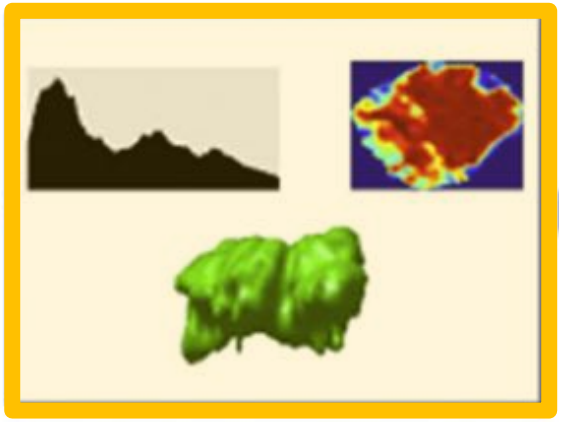


Image collection



Segmentation



Features extraction

Analysis and modeling

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Radiomics: features extraction

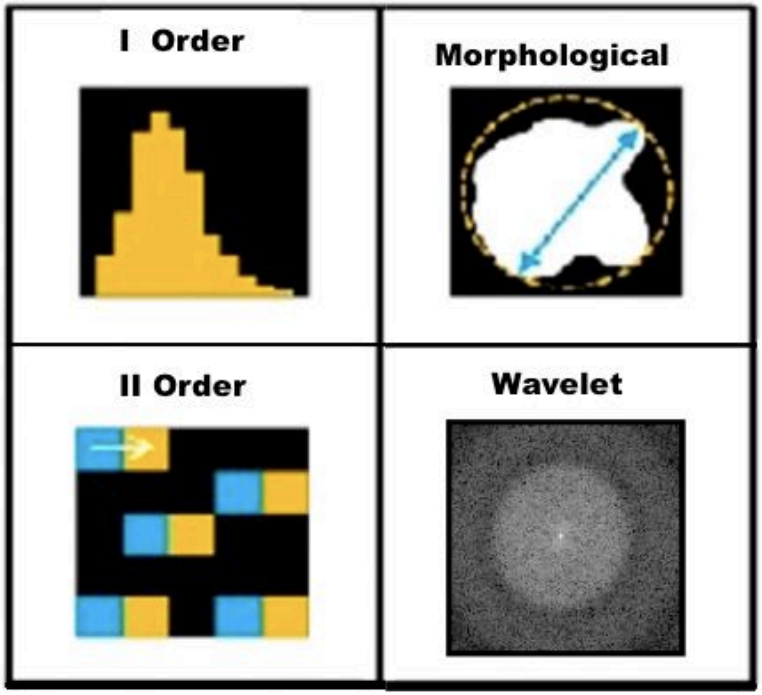
Features categories:

STATISTICAL

Mean, Median, Skewness, Entropy, Kurtosys

TEXTURE ANALYSIS

Autocorrelation, Cluster Prominence, Cluster Shade



SHAPE

Area, Volume, Compactness, Sphericity

WAVELET

Low frequencies, high frequencies

Information about pixels spatial distribution

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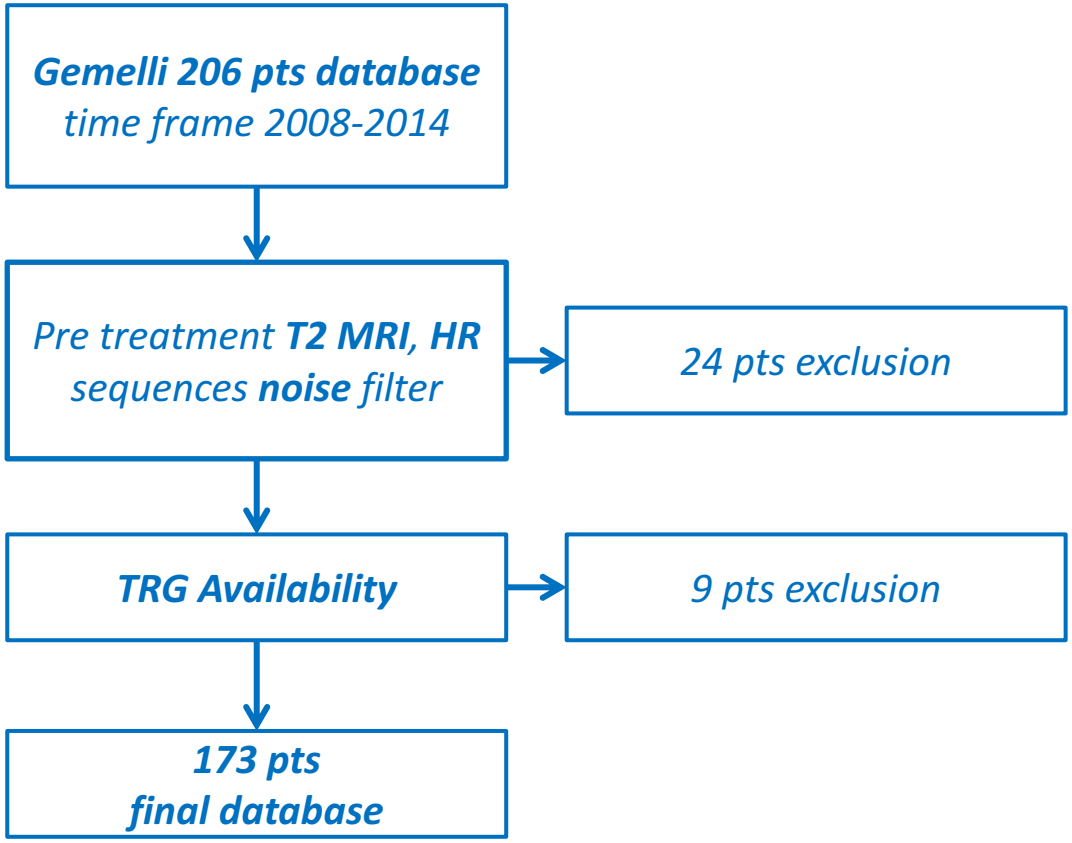
KBO Radiomics: rectal cancer experience



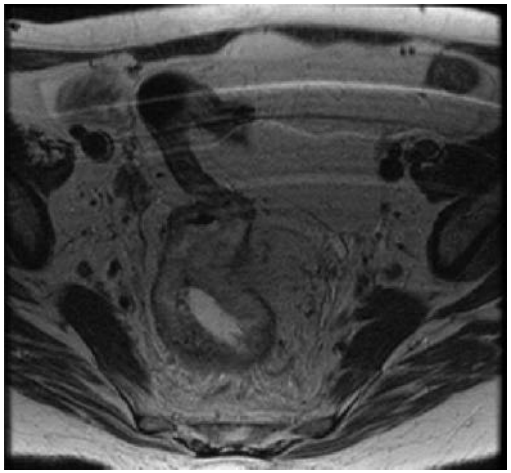
1. ROI extraction

2. Pre-processing:
- **LoG filter application**

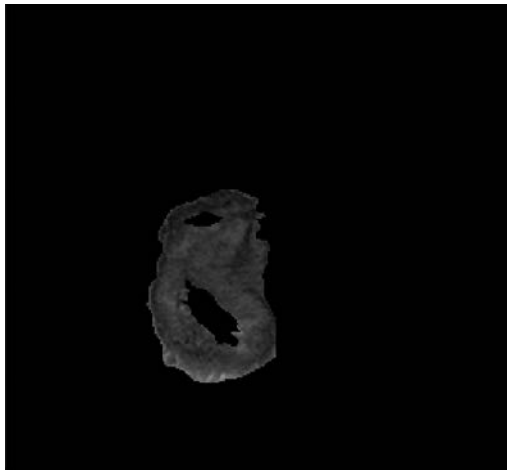
3. Data analysis (Moddicom):
- **Model construction**
- **Model validation**

KBO Radiomics: rectal cancer experience

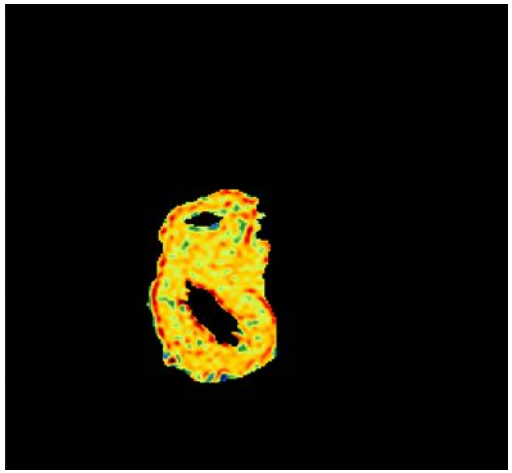
MRI



ROI extraction



Filter application



Kurtosis, Skewness, Entropy

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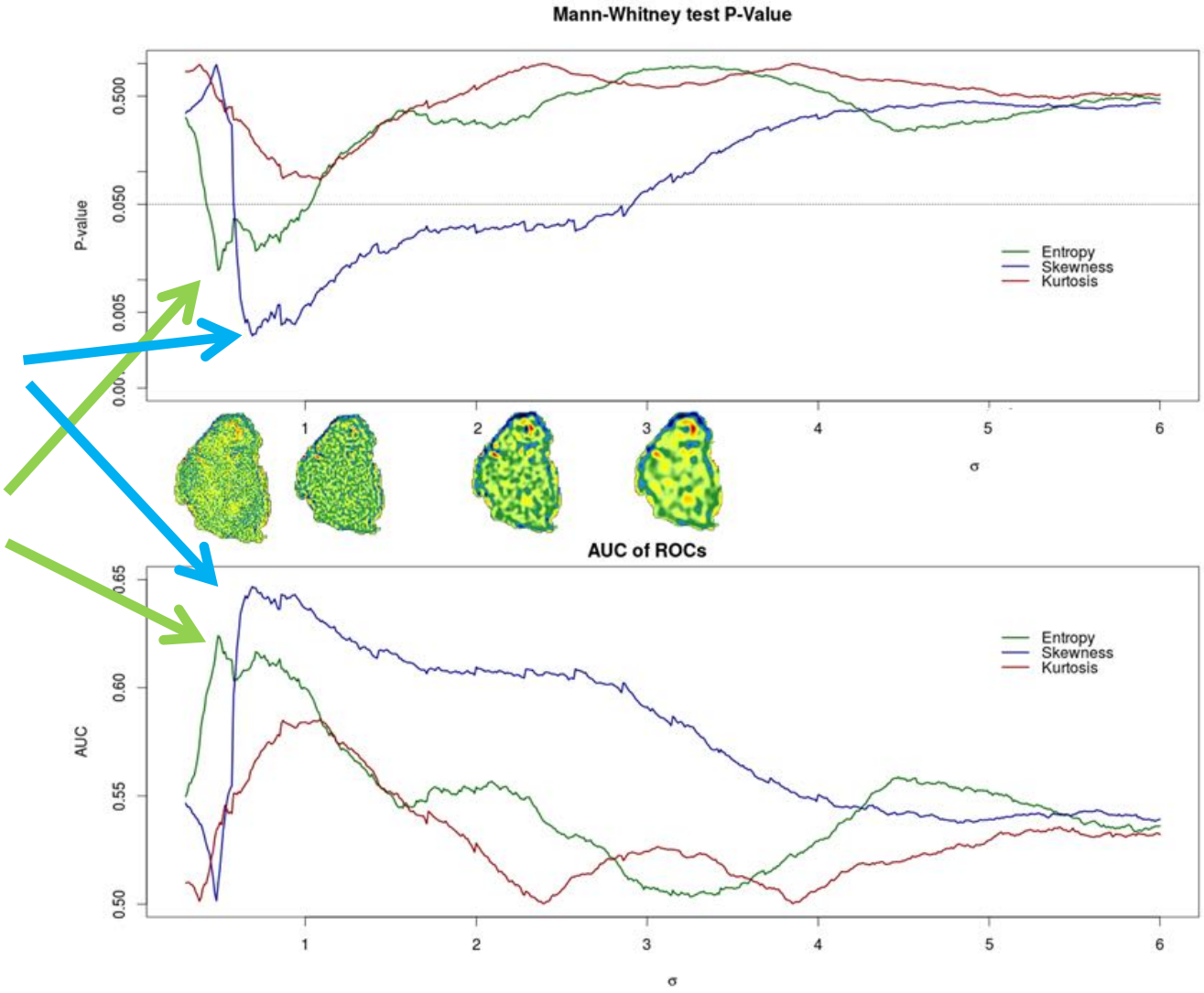
KBO Radiomics: rectal cancer experience



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KBO Radiomics: rectal cancer experience

The following variables were evaluated with multivariate logistic analysis for 173 rectal cancer patients

cT
cN
GTV Volume
GTV Surface
Equivalent Sphere Volume / GTV Surface
Entropy s = 0.49
Skewness s = 0.69

Final model:
Coefficients:

	Estimate	Std. Error	z value	Pr(>|z|)	
(Intercept)	-5.1466	3.9229	-1.312	0.18954	
cT	-1.0442	0.3584	-2.913	**0.00358**	**
cN	0.5350	0.3412	1.568	0.11689	
Entropy Sigma	0.49	3.2354	1.6420	1.970	**0.04880** *
Skewness Sigma	0.69	-3.1480	1.1601	-2.714	**0.00666** **

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

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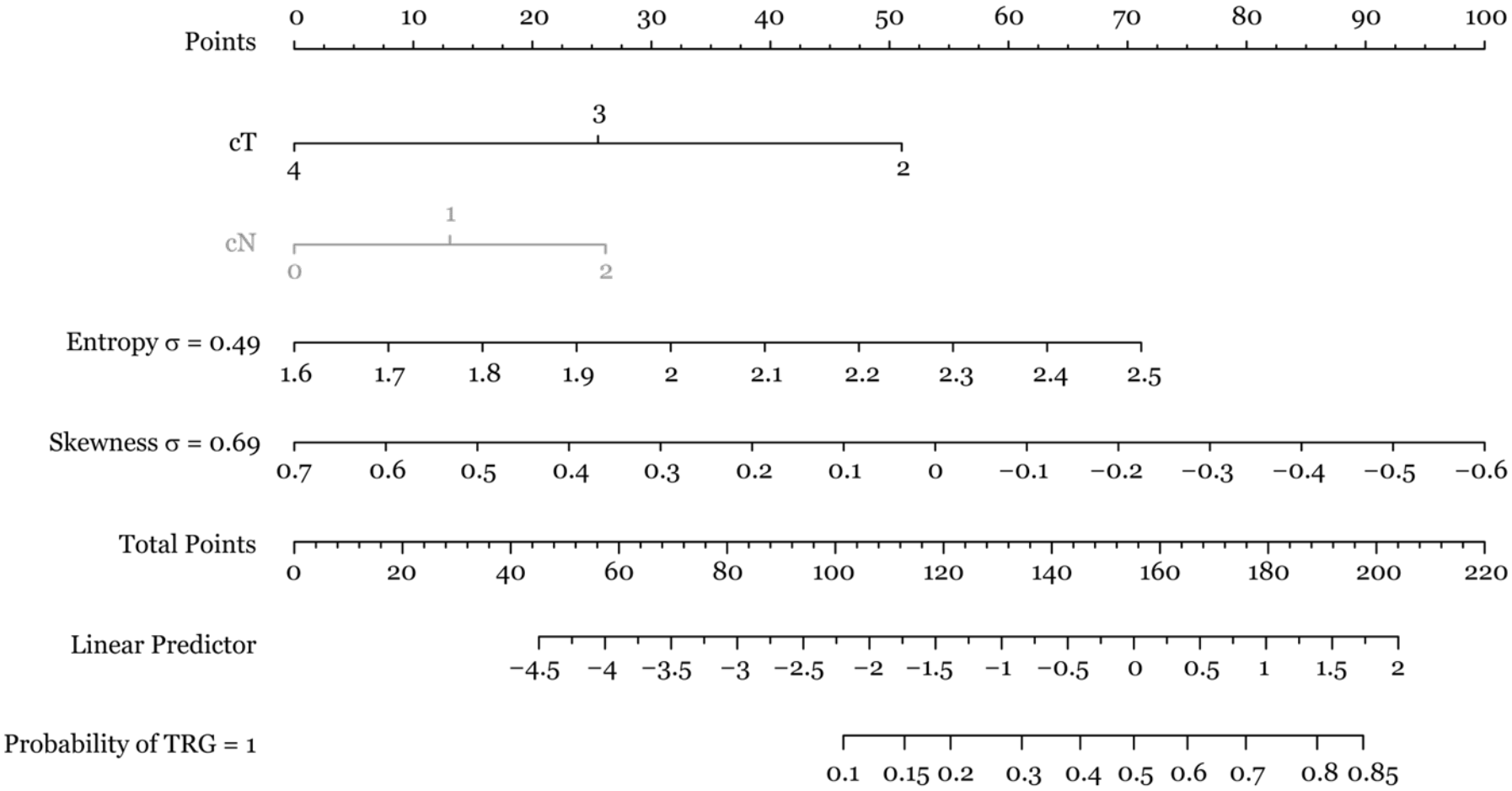
From Radiomics to nomograms



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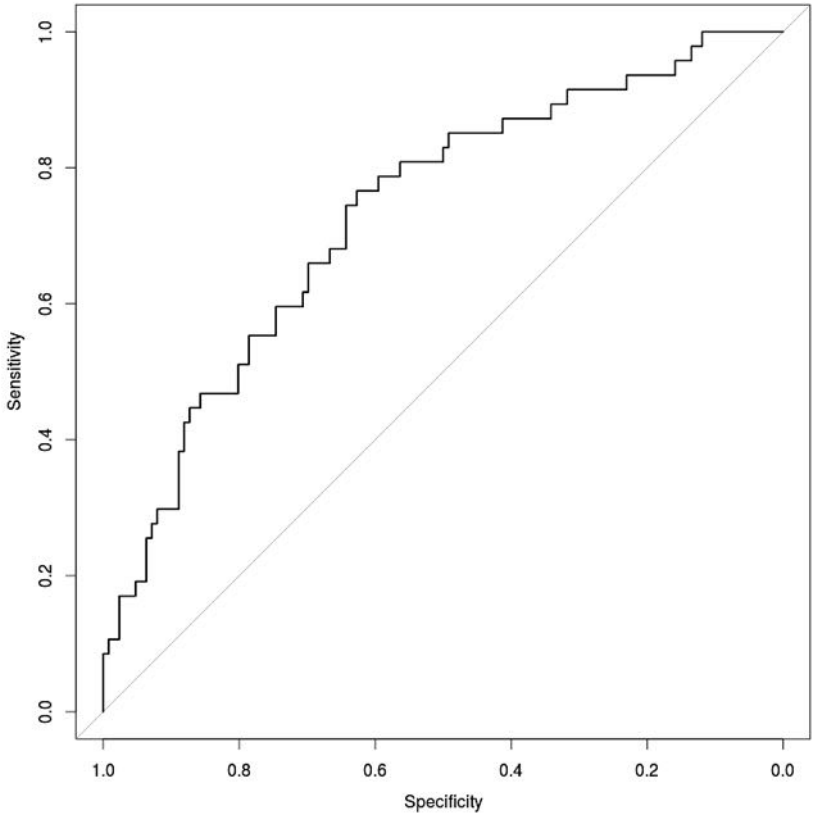
Internal validation

5000 bootstrap resampling

TRIPOD 1b

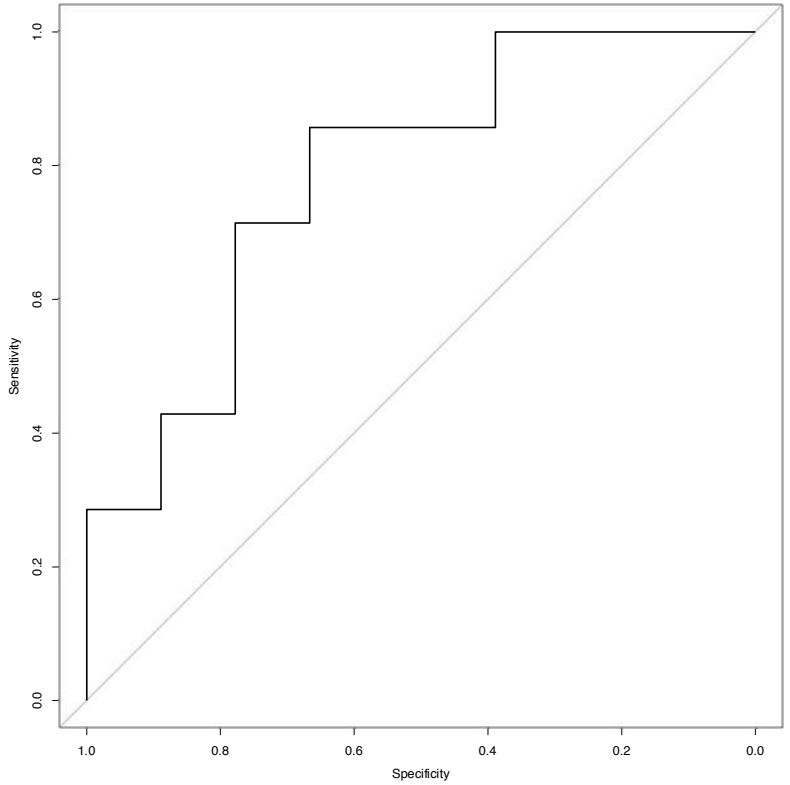


AUC = 0.73

External validation

25 cases MAASTRO

TRIPOD 3



AUC = 0.77

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KBO Radiomics: rectal cancer experience

Internal validation

KBO

173 Patients

47/173 pCR (28%)

T2-w

Slice thickness 3 mm

RM GE Signa Exite @1.5 T

External validation

MAASTRO

25 Patients

7/25 (26%)

T2-w

Slice thickness 3 mm

RM Achieva @ 1.5 T

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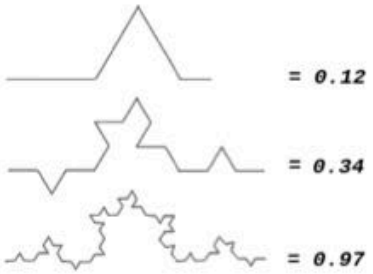
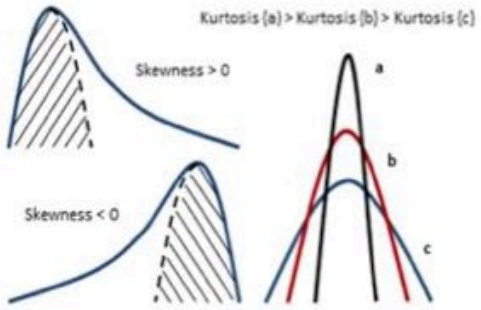
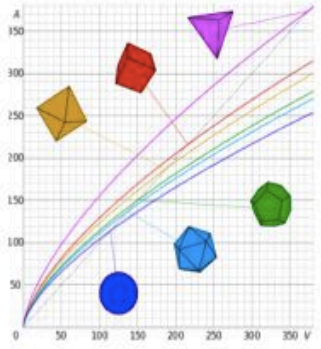
KBO Radiomics: features extraction



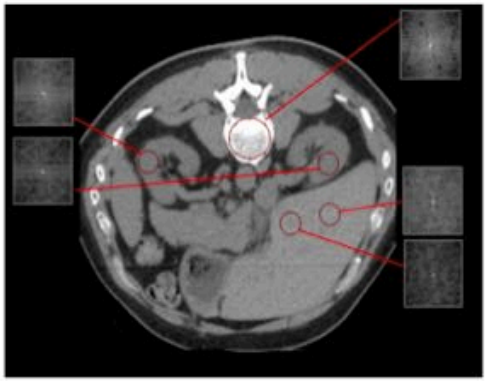
Fractal dimension



Grey-level Histogram Measures, (i.e. Kurtosis, Skewness, ...)



Voume/surface ratio



Local Granularity

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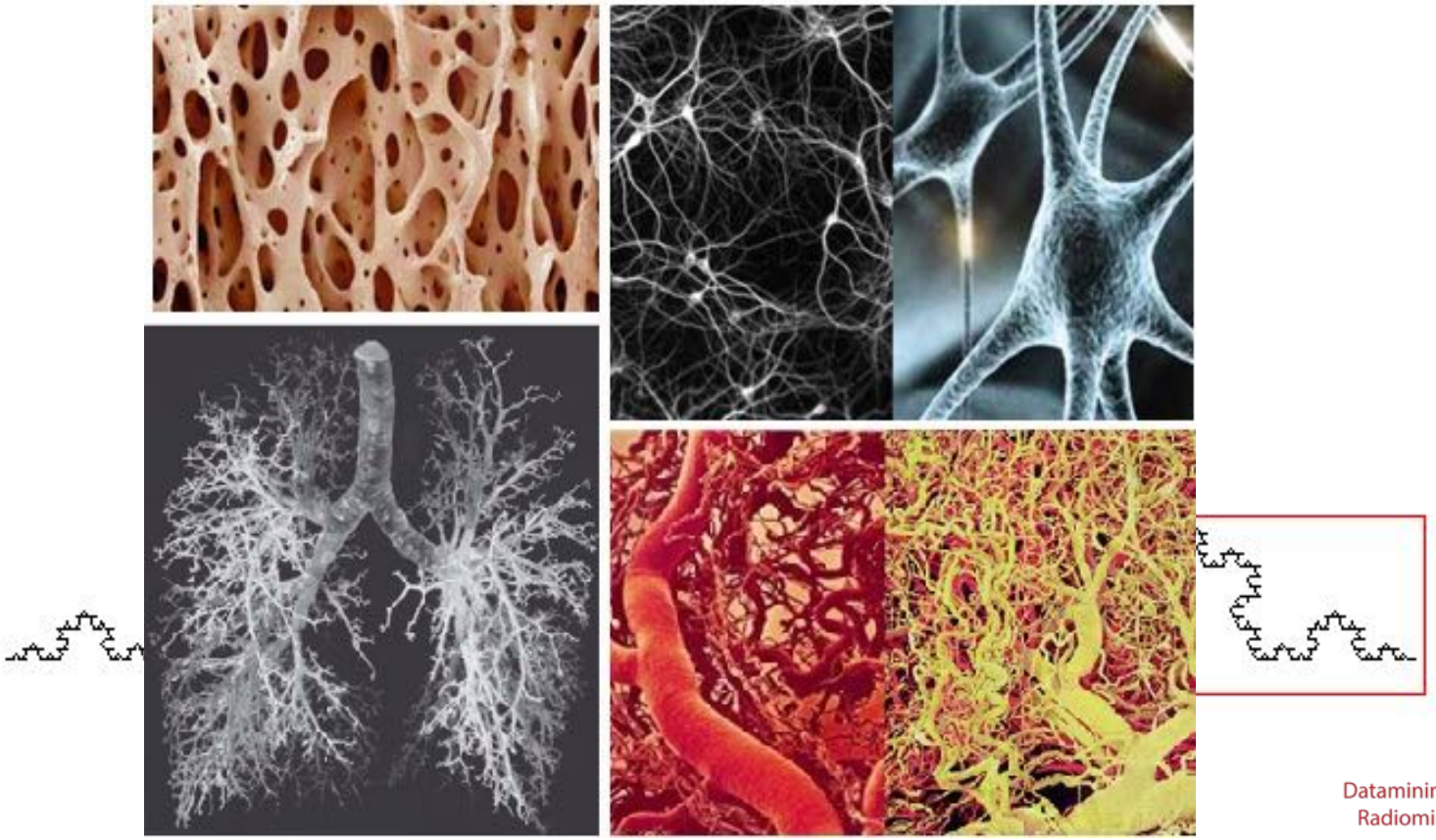
Fractals

Object that presents the same weave on different scales

scale invariance



Ponteconi et al, 2016; Cross et al, 1998; Waliszewski P, 2016

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Fractal dimension

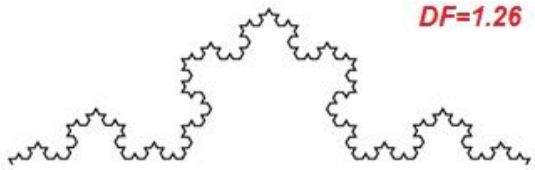
The parameter that characterizes a fractal is the fractal dimension

Measure of object's complexity

$$S(x) = x^{DF} \qquad 1 < DF < 2$$

Low FD

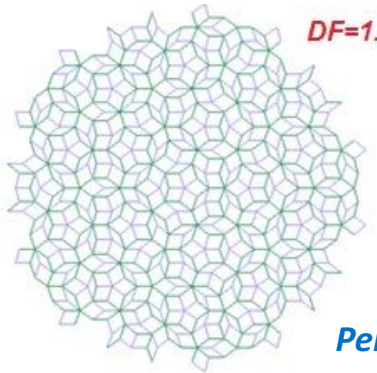
Pronged system



Koch curve

High FD

Compact system



Penrose distribution

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Mandelbrot B. *The fractal geometry of nature.* 1982

KBO Radiomics: features extraction

Introduction of Fractal Dimension

x_i	α_i	$\sigma(\alpha_i)$	p-value
Intercept	11.366	6.119	0.063
cT	-0.997	0.377	**0.007**
cN	0.619	0.359	0.084
Skewness (σ=0.48)	-3.601	1.361	**0.008**
Entropia (σ=0.34)	2.948	1.719	0.086
Max DF (40-100)	-9.862	3.228	**0.002**

cT

Tumor Extension

↑ cT ↓ pCR

Skewness

Histogram Slope

↑ S ↓ pCR

Max DF

Subpopulation 40-100

↑ maxDF ↓ pCR

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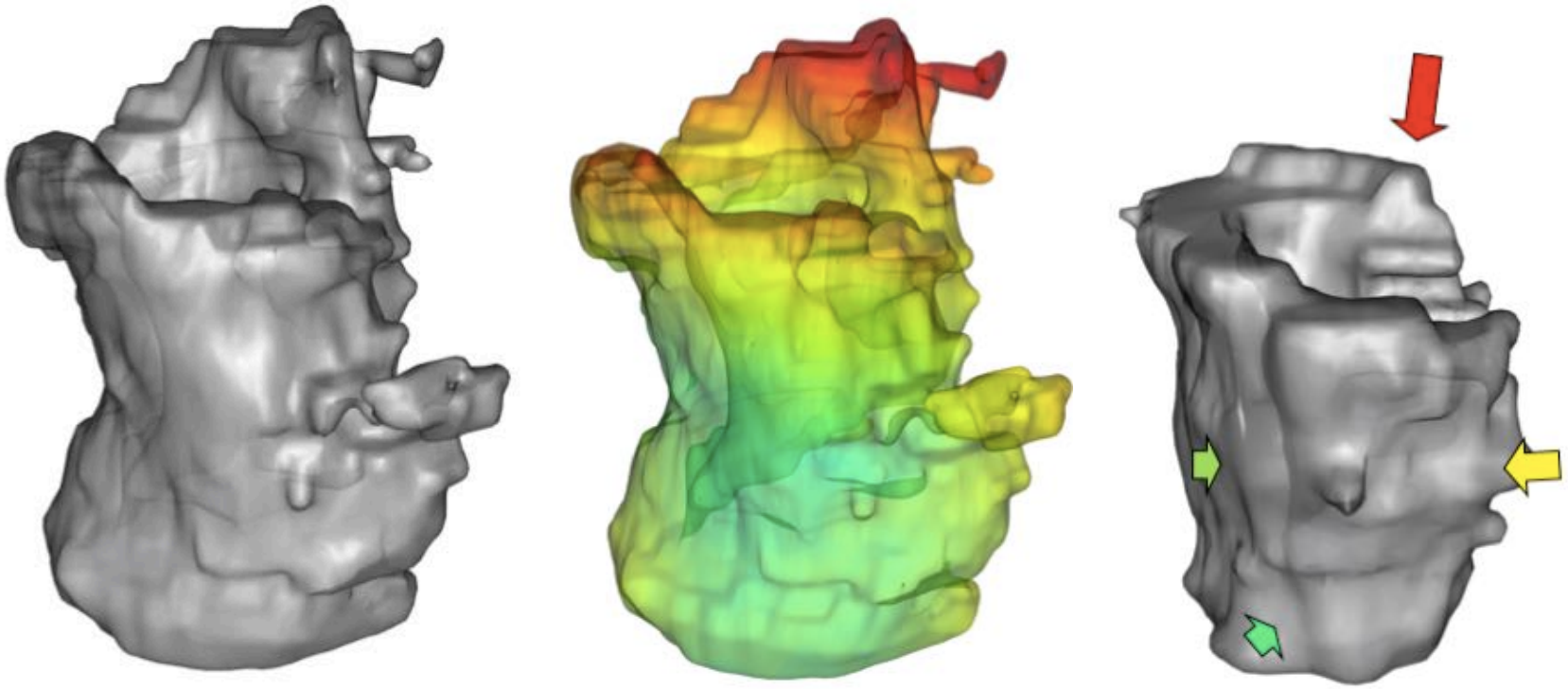
Personalization by Radiomics



GTV Pre

Distance heatmap

GTV Post

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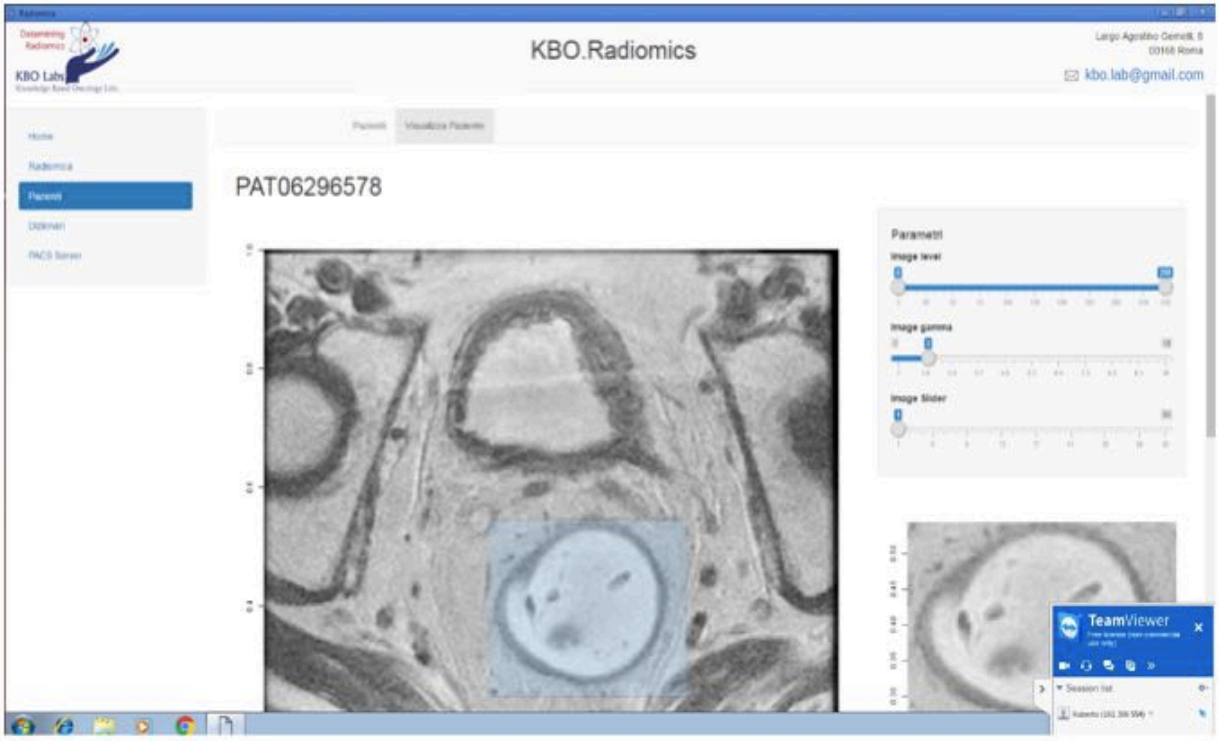
KBO Radiomics: features extraction

KBO.Radiomics (*personal edition*) is a *free* and *open source* software tool, **"easy to use",** to facilitate the firsts steps in the world of Radiomics analysis.



Microsoft Windows

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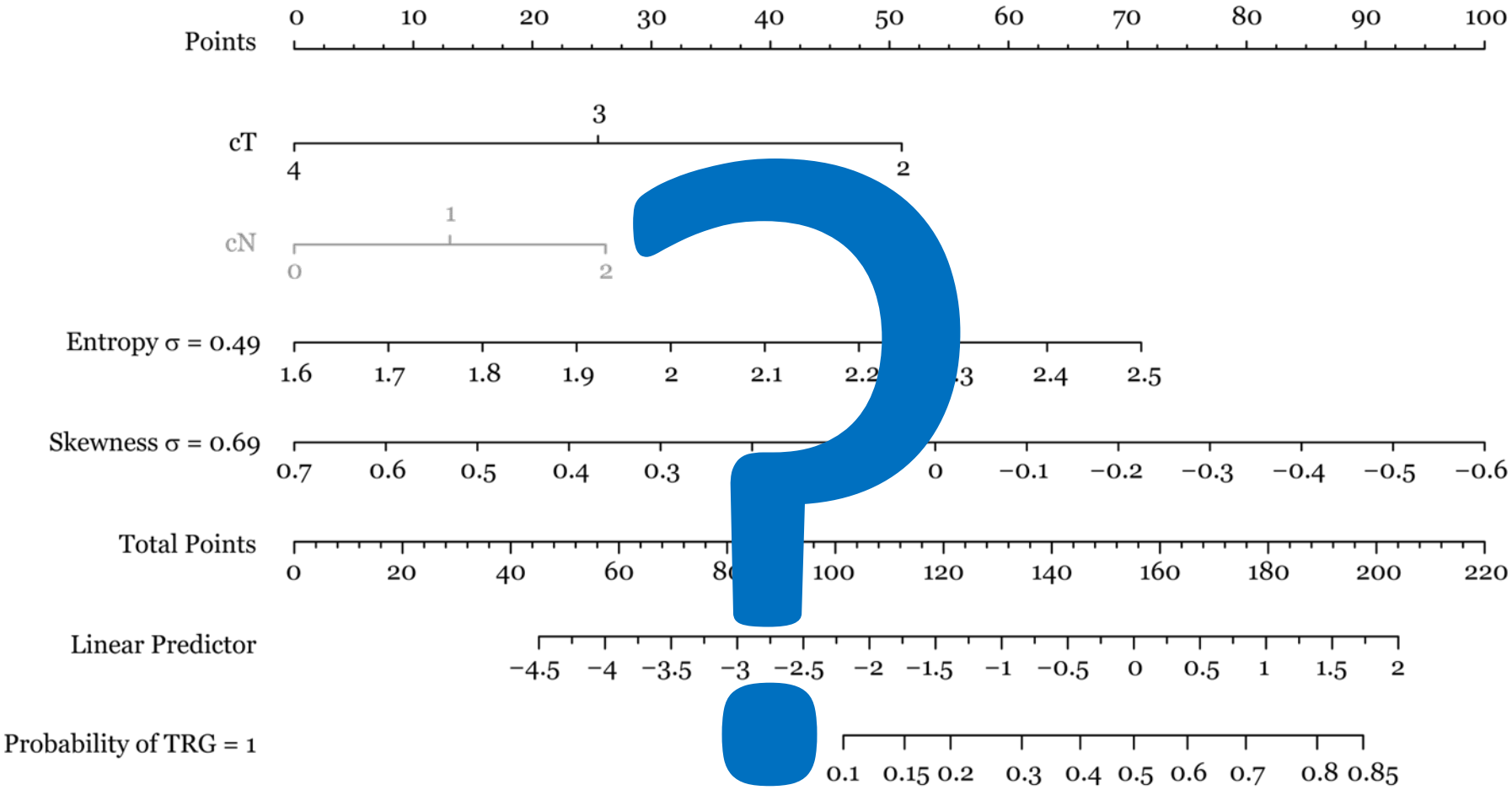
From Radiomics to nomograms



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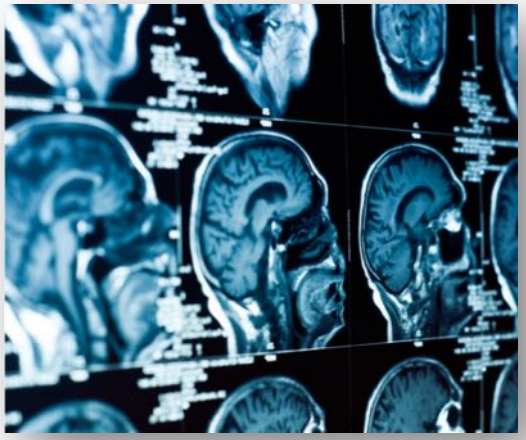
Data sharing

Data from different sources and contexts could highly improve our knowledge

Clinical Data

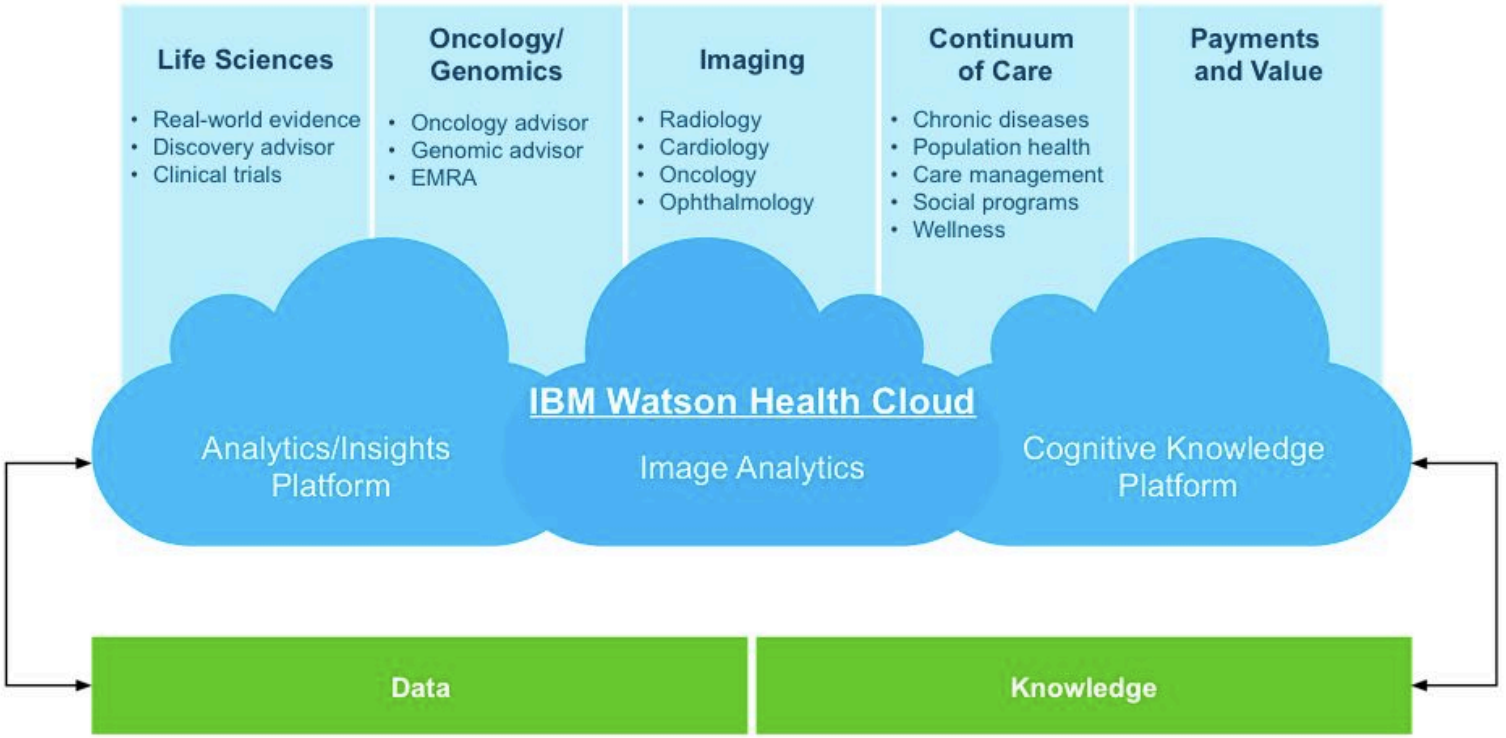
Genetics

Imaging Data



Lambin P. et al - Eur J Cancer - 2012
Valentini V. et al - J Clin Oncol - 2011

Five pillars enabled through a platform that has data, knowledge, analytics and industry specific solutions supported on a secure cloud.



Data sharing

*What we would **need** to share*

*What we are **willing** to share*

*What we are **able** to share*

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Radiomics

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Data sharing

Which barriers?

Table 1 Evidence for barriers to sharing of routinely collected public health data

Category	Barrier	Peer-reviewed		Non peer-reviewed
		Empirical data	Non-empirical*	
Technical	1. Data not collected	[6,21,24,31]	[2,4,7,18,22,14,26-28,30]	[3,23,25]
	2. Data not preserved		[33]	[3,32,34,35]
	3. Data not found		[45]	[3,34]
	4. Language barrier			[36]
	5. Restrictive data format		[40]	[3,34,36-39,41]
	6. Technical solutions not available		[42]	[37]
	7. Lack of metadata and standards	[21,24,43]	[40,44,45]	[1,35-37,39,41,46]
Motivational	8. No incentives		[27,45,49]	[35]
	9. Opportunity cost	[51,52]	[13,33,50,53]	[35]
	10. Possible criticism		[33]	[32]
	11. Disagreement on data use	[21]	[49]	
Economic	12. Possible economic damage		[7,26,27,30]	[55]
	13. Lack of resources	[56,21]	[13,27,28,30,42,53,57]	[3,23,34-36,39,37]
Political	14. Lack of trust	[19,59,60]	[33,61]	[34-37]
	15. Restrictive policies		[30]	
	16. Lack of guidelines		[45,62,65]	[37,41,63,64]
Legal	17. Ownership and copyright		[62,65,66,69]	[37,63,64,67]
	18. Protection of privacy	[12,19,59,73,75]	[44,57,62,66,72,74]	[36,37,64,67,68,70,71]
Ethical	19. Lack of proportionality			[76]
	20. Lack of reciprocity	[51,52]	[50,77,78]	
Number of unique documents (% of total)		14 (21.5%)	30 (46.2%)	21 (32.3%)

**No or little original data presented.*

Willem et a*l BMC Public Health, 2014*

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Data sharing

Benefits

- transparency and cooperation
- reproducibility of research
- cost-efficiency
- preventing redundancies
- acceleration of discovery and innovation
- making more efficient and effective public health programs

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Imaging and Interventional Radiology for Radiation Oncology

Editors: Regina G.H. Beets-Tan, Wim Oyen, Vincenzo Valentini

Part I : **Imaging in Oncology: from diagnosis to outcomes**
Part II : **From simulation to delivery guided by imaging: technical aspects**
Part III : **Imaging for tumor staging and volume definition**
Part IV : **Response evaluation and Follow up by Imaging**

Springer

Looking to (a near) future

- *New segmentation and planning techniques (e.g. imaging biomarkers)*
- ***New paradigms of IGRT and adaptive real time RT***
- *New hybrid techniques and machines*
- ***New prognostic stratification systems and clinical decision tools***
- *New radiomics perspectives and clinical integration*

KBO Acknowledgments

- *Coordinators*

  V. Valentini, A. Damiani

- *PhDs*

  A.R. Alitto, S. Chiesa, G. Chiloiro, D. Cusumano

  N.Dinapoli, A. Farchione, R.Gatta, V.Lanni

  J. Lenkowicz, G.C.Mattiucci, C.Masciocchi, E. Meldolesi

- *Collaboration with MAASTRO Clinic*

  A. Dekker, J. Van Soest, P. Lambin

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MAASTRO